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(71) Applicant
**American Cyanamid Company**

**(Incorporated in the USA-Maine)**

**Berdan Avenue, Township of Wayne,**
**State of New Jersey 06904, United States of America**

(72) Inventors
**Michael Peter Ramsey**
**Amer Ahmed Alsaden**

(74) Agent and/or Address for Service
**Lloyd Wise Tregear & Co**
**Norman House, 105-109 Strand, London, WC2R 0AE,**
**United Kingdom**

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# (54) Stabilised neomycin solutions

(57) The stability of pharmaceutical compositions containing neomycin or neomycin salt and sodium metabisulphite dissolved in a non-aqueous liquid vehicle is improved by the addition of a pharmaceutically acceptable organic amine, preferably tris-(hydroxymethyl)-aminomethane. The liquid vehicle is preferably propylene glycol and the composition is adjusted to a pH of 3 to 5 e.g. by addition of benzoic acid. An anti-inflammatory agent such as triamcinolone acetonide may also be present. The stabilised composition when it contains 0.25-0.5% w/v of neomycin and of sodium metabisulphite is suitable for treating otitis.

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# NEOMYCIN-CONTAINING PHARMACEUTICAL COMPOSITIONS

This invention relates to pharmaceutical compositions which contain neomycin, or a salt thereof, in a non-aqueous vehicle, and is concerned with improving the stability of such compositions.

Neomycin is an antibiotic having antibacterial properties which finds use in the treatment of a number of conditions, by itself or in conjunction with other therapeutic agents e.g. steroids. Currently, neomycin is used in the form of a pharmaceutically acceptable salt, rather than as the free base. The present invention is concerned with improving the stability of neomycin-containing preparations which are formulated as solutions in non-aqueous liquid vehicles.

One such preparation which has found widespread acceptance for the treatment of acute and chronic otitis externa where bacterial or fungal infection is present is manufactured by us under the trade mark "Audicort". Essentially, the "Audicort" preparation consists of neomycin, as its undecylenate, and triamcinolone acetonide (an anti-inflammatory agent) dissolved in propylene glycol, and is normally presented in a stoppered container for administration as drops into the external auditory canal of a patient. An antioxidant, sodium metabisulphite by choice, is also incorporated into the "Audicort" preparation to prevent oxidation of the active ingredients, especially neomycin which is sensitive to oxidation.

It is observed that a white precipitate may form in neomycin-containing preparations during their 18 month shelf-life. This undesirable phenomenon is accompanied by a loss of neomycin potency, typically of the order of 20% over 18 months. Following detailed investigations which we have conducted, it is surmised

that the sodium metabisulphite antioxidant itself oxidizes on storage to liberate sulphate ions which interact with neomycin base to form neomycin sulphate which is insoluble in the propylene glycol vehicle.

The present invention seeks to provide non-aqueous neomycin-containing solutions which have improved stability as shown by a reduced tendency to precipitate formation and improved retention of neomycin potency, even when protected from oxidation by sodium metabisulphite.

In accordance with this invention, it has been found that the addition of an organic base to sodium metabisulphite-protected non-aqueous neomycin-containing pharmaceutical preparations leads to a significant improvement in the stability of such preparations under normal conditions of storage.

Thus, the present invention broadly provides a pharmaceutical composition comprising neomycin, or a pharmaceutically acceptable salt thereof, dissolved in a non-aqueous liquid vehicle, sodium metabisulphite as an antioxidant for said neomycin or neomycin salt, and a pharmaceutically acceptable organic amine as a stability-improving agent.

Our investigations have demonstrated that the stability-enhancing effects can be achieved with a wide variety of different amines and appear to be independent of the position or number of amine groups within the molecule. Thus, any organic amine which is pharmaceutically acceptable can be used in the compositions of this invention. Examples of such amines are hydroxyamines such as tris-(hydroxymethyl)--aminomethane (hereafter TRIS for short), mono-, di- and tri-ethanolamine, diisopropanolamine and N-methyl-D--glucamine.

The amount of amine to be incorporated to achieve a worthwhile improvement in stability will, of course, depend on the concentrations of neomycin and antioxidant in the preparation. Known preparations such as the aforementioned "Audicort" ear drops typically contain from 0.25% to 0.5% w/v of neomycin (calculated as the free base) and from 0.25% to 0.5% w/v of sodium metabisulphite. We have found that for such preparations it is preferred to incorporate 1-5 M, more preferably 1 to 2 M, of amine per mole of neomycin in order to achieve a significant improvement in stability.

It is found that on storage the compositions of this invention exhibit a continuing fall in pH due to the liberation of hydrogen ions during oxidation of the sodium metabisulphite. However, too low a pH can adversely affect physiological tolerance by the patient. For example, for administration into the external auditory canal, it is desired that the pH should not be below pH 3. The risk of an undesirably large drop in pH can be counteracted by adding an organic acid to the compositions of this invention to produce a buffer system in solution. Suitable organic acids are those which have sufficient solubility in the non-aqueous liquid vehicle to reach the desired buffer concentration and are compatible with neomycin in solution, and, of course, which are pharmaceutically acceptable. Examples of such acids include acetic acid, adipic acid, benzoic acid, boric acid, fumaric acid, salicyclic acid and succinic acid. Benzoic acid is preferred because of its excellent pharmaceutical and physiological acceptability.

The concentration of organic acid required to achieve complete buffering is, of course, dependent upon the extent of hydrogen ion generation to be expected, but typically will be within the range of 0.01-0.25M,

preferably about 0.1M, to achieve a pH within the range of 3 to 5.

A wide variety of non-aqueous vehicles can be employed as solvents for the neomycin salt, provided of course that they are pharmaceutically acceptable. Examples of particularly suitable non-aqueous vehicles are polyethylene glycol (MW 200-600) and glycerol. Propylene glycol is presently preferred.

The pharmaceutical compositions of this invention may, of course, contain other compatible active ingredients eg steroids and local anesthetics, or other excipients for specific purposes as well known in the art. Although the compositions are essentially non-aqueous, a small amount of water, typically about 2% v/v, may be used as a vehicle for the addition of the sodium metabisulphite, or other components, to the bulk of the composition.

It is postulated that the addition of the organic amine improves the stability of the present compositions by preferentially complexing with sulphate ions, thus preventing the formation of neomycin sulphate.

The invention is illustrated by the Examples which follow.

## Example 1

A preparation suitable for use as ear drops in the treatment of otitis externa was prepared with the following composition:

| | |
|---|---|
| triamcinolone acetonide | 0.105% w/v |
| neomycin undecylenate | 0.386% w/v (as base) |
| TRIS | 1.250% w/v |
| disodium edetate BP* | 0.060% w/v |
| sodium metabisulphite | 0.500% w/v |
| sterile water USP | 2.000% v/v |
| propylene glycol BP | to 100% |

pH adjusted to 3.5-4.5 using analar HCl

*this excipient is incorporated as chelating agent for metal ions.

First, a major portion of the propylene glycol was placed in a container and heated to 45-50°C. TRIS was now added, with stirring. When the TRIS had completely dissolved, the pH was adjusted to pH 3.5-4.5 using concentrated hydrochloric acid. Next, disodium edetate, previously dissolved in half the volume of distilled water, was added to the solution, followed by triamcinolone acetonide and neomycin undecylenate until completely dissolved. The pH was again adjusted to pH 3.5-4.5 with conc. HCl. Sodium metabisulphite, dissolved in the remaining portion of distilled water, was now added to the solution, and then the remainder of the propylene glycol was added. Finally, the pH was again adjusted to pH 3.5-4.5 with concentrated hydrochloric acid.

From the addition of the TRIS to the final pH adjustment, the solution was maintained under a blanket of nitrogen.

The clear, essentially colourless, solution which was formed was filled into 10 ml polyethylene bottles and sealed under nitrogen.

Two separate batches of the solution were prepared as above, and their stability was tested at 23°C, 37°C and 42°C over a period of 8 weeks (Batch I) and 4 weeks (Batch II). Even under the accelerated storage conditions at 37°C and 42°C, there was no significant loss of neomycin potency, the largest fall recorded (storage at 37°C for 8 weeks) being no more than 5.4% The solutions remained clear and colourless throughout, with no evidence of precipitation. There was little or no loss of triamcinolone acetonide activity in any of these stability tests, but the concentration of sodium metabisulphite in the solutions

fell markedly at the higher storage temperatures, due to oxidation of this compound, whilst the pH also fell, particularly at the higher temperatures, due to the regeneration of free $H^+$ species.

Example 2

Two further batches of an ear drop preparation were made following the general procedure of Example 1. The composition of the preparation was as given in Example 1 except that the concentration of sodium metabisulphite was 0.320% w/v. The stability of the neomycin undecylenate in these batches was tested, with the results as given in Table 1 below.

Table 1

| Storage Time Temp (°C) Weeks | Batch I NEOMYCIN | | | Batch II NEOMYCIN | | |
|---|---|---|---|---|---|---|
| | mg/ml | % I | % LC | mg/ml | % I | % LC |
| Label Claim (LC) | 3.50 | | | 3.50 | | |
| Theory | 3.86 | | | 3.86 | | |
| Initial (I) | 3.90 | - | 111.4 | 4.12 | - | 117.7 |
| 37° 2 | 3.78 | 96.9 | 108.0 | 3.96 | 96.1 | 113.1 |
| 4 | 3.45 | 88.5 | 98.6 | 3.78 | 91.7 | 108.0 |
| 8 | 3.61 | 92.6 | 103.1 | 3.59 | 87.1 | 102.6 |
| 12 | 3.63 | 93.1 | 103.7 | 3.47 | 84.2 | 99.1 |
| 16 | 3.42 | 87.7 | 97.7 | 3.47 | 84.2 | 99.1 |
| 26 | 2.80 | 71.8 | 80.0 | 2.79 | 67.7 | 79.7 |
| 23° 2 | 3.95 | 101.3 | 112.9 | 4.15 | 100.7 | 118.6 |
| 4 | 3.57 | 91.5 | 102.0 | 3.78 | 91.7 | 108.0 |
| 8 | 3.76 | 96.4 | 107.4 | 3.97 | 96.4 | 113.4 |
| 12 | 3.79 | 97.2 | 108.3 | 3.92 | 95.1 | 112.0 |
| 16 | 3.73 | 95.6 | 106.6 | 3.86 | 93.7 | 110.3 |
| 26 | 3.80 | 97.4 | 108.6 | 3.93 | 95.4 | 112.3 |
| 3° 12 | 3.97 | 101.8 | 113.4 | 3.99 | 96.8 | 114.0 |
| 16 | 3.91 | 100.3 | 111.7 | 4.10 | 99.5 | 117.1 |
| 26 | 3.95 | 101.3 | 112.9 | 4.08 | 99.0 | 116.6 |
| 37R 2 | 3.87 | 99.2 | 110.6 | 3.95 | 95.9 | 112.9 |
| 4 | 3.47 | 89.0 | 99.1 | 3.86 | 93.7 | 110.3 |
| 8 | 3.68 | 94.4 | 105.1 | 3.57 | 86.7 | 102.0 |
| 12 | 3.29 | 84.4 | 94.0 | 3.27 | 79.4 | 93.4 |
| 16 | 3.42 | 87.7 | 97.7 | 3.42 | 83.0 | 97.7 |
| 26 | 2.65 | 67.9 | 75.7 | 3.48 | 84.5 | 99.4 |

From the stability data for neomycin presented in Table 1 it can be deduced that under normal storage conditions the potency of the neomycin would not fall below about 95% of its label value over a period of about 18 months.

Example 3

Four batches of an ear drop preparation were made following the general procedure of Example 1. The composition of the preparation was as set forth in Example 1, except that the concentration of sodium metabisulphite was 0.320% w/v, that undecylenic acid was added to achieve a standard concentration, and that 1.22% w/v of benzoic acid USP was incorporated, at the same time as the addition of the TRIS, as a buffer. In the preparation of these four batches, the pH was maintained within the range of 4.5-5.0 using, as appropriate either conc. HCl. or NaOH.

The stability of these benzoic acid-buffered preparations was tested, and the results are given in Table 2.

Table 2

| Storage Time Temp(°C) Weeks | | Batch I | | | Batch II | | |
|---|---|---|---|---|---|---|---|
| | | mg/ml | % I | % LC | mg/ml | %I | % LC |
| Label Claim (LC) | | 3.50 | | | 3.50 | | |
| Theory | | 3.85 | | | 3.85 | | |
| Initial (I) | | 3.63 | - | 103.7 | 3.93 | - | 112.3 |
| 37 | 4 | 3.27 | 90.1 | 93.4 | 4.07 | 103.6 | 116.3 |
| | 8 | 3.42 | 94.3 | 97.7 | 3.76 | 95.7 | 107.4 |
| | 12 | 3.08 | 84.8 | 88.0 | 3.94 | 100.3 | 112.6 |
| | 16 | 2.53 | 69.7 | 72.3 | - | - | - |
| | 26 | 3.02 | 83.2 | 86.3 | 3.08 | 78.4 | 88.0 |
| 23 | 4 | - | - | - | 4.02 | 102.3 | 114.9 |
| | 8 | 3.58 | 98.6 | 102.3 | - | - | - |
| | 12 | 3.54 | 97.5 | 101.1 | 3.92 | 99.7 | 112.0 |
| | 16 | 3.60 | 99.2 | 102.9 | - | - | - |
| | 26 | 3.40 | 93.7 | 97.1 | 4.08 | 103.8 | 116.6 |
| 3 | 26 | - | - | - | - | - | - |
| 37R | 4 | 3.32 | 91.5 | 94.9 | 3.88 | 98.7 | 110.9 |
| | 8 | - | - | - | - | - | - |
| | 12 | 3.38 | 93.1 | 96.6 | 3.86 | 98.2 | 110.3 |
| | 16 | - | - | - | - | - | - |
| | 26 | 1.66 | 45.7 | 47.4 | - | - | - |
| S/L * | 4 | - | - | - | - | - | - |
| | 12 | - | - | - | - | - | - |
| | 26 | - | - | - | - | - | - |

* S/L stands for sunlight

Table 2 (continued)

| Storage Time Temp (°C) Weeks | | Batch III | | | Batch IV | | |
|---|---|---|---|---|---|---|---|
| | | mg/ml | % I | % LC | mg/ml | % I | % LC |
| Label Claim (LC) | | 3.50 | | | 3.50 | | |
| Theory | | 3.85 | | | 3.85 | | |
| Initial (I) | | 4.01 | - | 114.6 | 4.00 | - | 114.3 |
| 37 | 4 | 3.83 | 95.5 | 109.4 | 3.92 | 98.0 | 112.0 |
| | 8 | 3.85 | 96.0 | 110.0 | 3.82 | 95.5 | 109.1 |
| | 12 | 3.68 | 91.8 | 105.1 | 3.98 | 99.5 | 113.7 |
| | 16 | 3.48 | 86.8 | 99.4 | 4.09 | 102.3 | 116.9 |
| | 26 | 2.82 | 70.3 | 80.6 | - | - | - |
| 23 | 4 | 4.00 | 99.8 | 114.3 | 4.00 | 100.0 | 114.3 |
| | 8 | 4.01 | 100.0 | 114.6 | 3.90 | 97.5 | 111.4 |
| | 12 | 3.98 | 99.3 | 113.7 | 4.19 | 104.8 | 119.7 |
| | 16 | 3.84 | 95.8 | 109.7 | 4.08 | 102.0 | 116.6 |
| | 26 | 3.64 | 90.8 | 104.0 | - | - | - |
| 3 | 26 | 3.89 | 97.0 | 111.1 | - | - | - |
| 37R | 4 | 3.90 | 97.3 | 111.4 | 3.89 | 97.3 | 111.1 |
| | 8 | 3.77 | 94.0 | 107.7 | 3.73 | 93.3 | 106.6 |
| | 12 | 3.81 | 95.0 | 108.9 | 4.02 | 100.5 | 114.9 |
| | 16 | 3.44 | 85.8 | 98.3 | 3.91 | 97.8 | 111.7 |
| | 26 | 2.14 | 53.4 | 61.1 | - | - | - |
| S/L* | 4 | - | - | - | 3.85 | 96.3 | 110.0 |
| | 12 | 3.98 | 99.3 | 113.7 | 4.15 | 103.8 | 118.6 |
| | 26 | 3.55 | 88.5 | 101.4 | - | - | - |

* S/L stands for sunlight

By comparing Table 1 with Table 2, it can be seen that the addition of the benzoic acid buffer does not adversely affect the stability of the compositions.

Example 4

To test the suitability of pharmaceutically acceptable amines for improving the stability of neomycin-containing, non-aqueous formulations, four batches of an ear drop preparation were made following the general procedure of Example 1. The composition of each formulation was as follows:

| | |
|---|---|
| micronised triamcinolone acetonide USP | 0.105% w/v |
| neomycin undecylanate (as neomycin base) | 0.385% w/v |
| undecylenic acid | 0.770% w/v |
| test amine | 1.250% w/v |
| benzoic acid USP | 1.22% w/v |
| disodium edetate USP | 0.060% w/v |
| sodium metabisulphite-reagent anhydous | 0.320% w/v |
| sterile water USP | 2.000% w/v |
| propylene glycol USP | to 100% w/v |
| pH adjusted to 3.8-4.7 using analar HCl or NaOH N.F. | |

The four test amines used were:

Batch I : TRIS
Batch II : Ethanolamine
Batch III : Diethanolamine
Batch IV : Triethanolamine

For comparison purposes, a further ear-drop preparation was made up which contained identical amounts of neomycin and sodium metabisulphite but no amine.

50 ml of each of the four batches in accordance with this invention and of the comparative batch were titrated with 0.5 ml aliquots of 1M sulphuric acid. The pH was measured after each addition, the end point being the formation of a sulphate precipitate.

The results are tabulated in Table 3 below:

Table 3

| Test Amine | Initial pH | pH at end point | Vol.(ml)$H_2SO_4$ added to end point |
|---|---|---|---|
| TRIS | 4.35 | 2.51 | 1.5 |
| Ethanolamine | 4.54 | 1.83 | 3.0 |
| Diethanolamine | 4.70 | 3.06 | 1.5 |
| Triethanolamine | 4.76 | 3.27 | 1.5 |
| None | 4.47 | 2.83 | 1.0 |

From Table 3 it can be seen that all the amines tested reduced the onset of sulphate precipitation as compared with the comparative batch which contained no amine. Of the four test amines used, ethanolamine improved the stability of the preparation to the greatest extent. Nonetheless, we currently prefer to use TRIS because of its biological tolerance.

CLAIMS:

1. A pharmaceutical composition comprising neomycin, or a pharmaceutically acceptable salt thereof, dissolved in a non-aqueous liquid vehicle, sodium metabisulphite as an antioxidant for said neomycin or neomycin salt, and a pharmaceutically acceptable organic amine as a stability-improving agent.

2. A composition according to Claim 1, suitable for administration as drops into the external auditory canal for the treatment of acute and chronic otitis, and comprising 0.25%-0.5% w/v of neomycin (calculated as the free base), 0.25%-0.5% of sodium metabisulphite, and from 1-5M of said organic base per mole of neomycin base.

3. A composition according to Claim 1 or Claim 2, wherein said neomycin salt is neomycin undecylenate and said liquid vehicle is propylene glycol.

4. A composition according to any preceding claim, wherein said organic base is tris-(hydroxymethyl)-aminomethane.

5. A composition according to any preceding claim, comprising also a pharmaceutically acceptable organic acid to buffer the composition to a pH within the range of 3 to 5.

6. A composition according to Claim 5, wherein said organic acid is benzoic acid.

7. A composition according to any preceding claim, comprising also an anti-inflammatory agent.

8. A composition according to Claim 7, wherein said anti-inflammatory agent is triamcinolone acetonide.

9. A pharmaceutical composition substantially as described in any one of the Examples herein.

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